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Review article

Dopamine across timescales and cell types: Relevance for phenotypes in Parkinson's disease progression

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ABSTRACT

Dopamine neurons in the substantia nigra pars compacta (SNc) synthesize and release dopamine, a critical neurotransmitter for movement and learning. SNc dopamine neurons degenerate in Parkinson's Disease (PD), causing a host of motor and non-motor symptoms. Here, we review recent conceptual advances in our basic understanding of the dopamine system – including our rapidly advancing knowledge of dopamine neuron heterogeneity – with special attention to their importance for understanding PD. In PD patients, dopamine neuron degeneration progresses from lateral SNc to medial SNc, suggesting clinically relevant heterogeneity in dopamine neurons. With technical advances in dopamine system interrogation, we can understand the relevance of this heterogeneity for PD progression and harness it to develop new treatments.

1. Introduction

The neurotransmitter dopamine is critical in the pathophysiology of Parkinson's disease (PD). The seminal discovery that reductions in dopamine produce the cardinal motor symptoms of PD led to a breakthrough treatment: the dopamine precursor L-DOPA. But more breakthroughs are needed. PD is now widely recognized as a multifaceted disorder, including motor and non-motor symptoms. While many of the core motor symptoms of PD respond well to L-DOPA, non-motor symptoms, such as cognitive impairment, are more challenging to treat. Dopamine replacement therapy does not resolve all PD symptoms, and chronic treatment often causes complications such as levodopa-induced dyskinesia. These shortcomings may be related to the importance of dopamine dynamics across space and time. L-DOPA and other pharmacological therapies cannot replicate the precisely calibrated targeting and timing of dopamine release supporting healthy behavior and dopamine-dependent synaptic plasticity.

To understand why L-DOPA cannot fully recapitulate natural dopamine dynamics in people with PD, we must consider its mechanism of action in combination with known patterns of dopamine neuron degeneration in PD. L-DOPA is converted to dopamine by aromatic L-amino acid decarboxylase (AADC) and can be released from intact dopamine terminals, but also from serotonergic terminals (Maeda et al., 2005; Tanaka et al., 1999). Multiple cell types express AADC (Arai et al., 1996; Kitahama et al., 1990), however, and it is unknown what circuit elements take up L-DOPA and release dopamine in advanced PD. Indeed, as degeneration proceeds, fewer and fewer intact dopamine terminals are available to release dopamine in natural patterns, which may drive worsening outcomes. It has long been known that dopamine neurons from different midbrain regions are selectively vulnerable to PD, and that axons terminating in striatal subregions degenerate at different rates (Surmeier et al., 2017). This observation suggests the pattern of dopamine release from converted L-DOPA may change over time, increasingly diverging from naturalistic patterns. As serotonergic neurons or other cell types start to take up and release dopamine, aberrant patterns of release may develop and drive abnormal dopamine-

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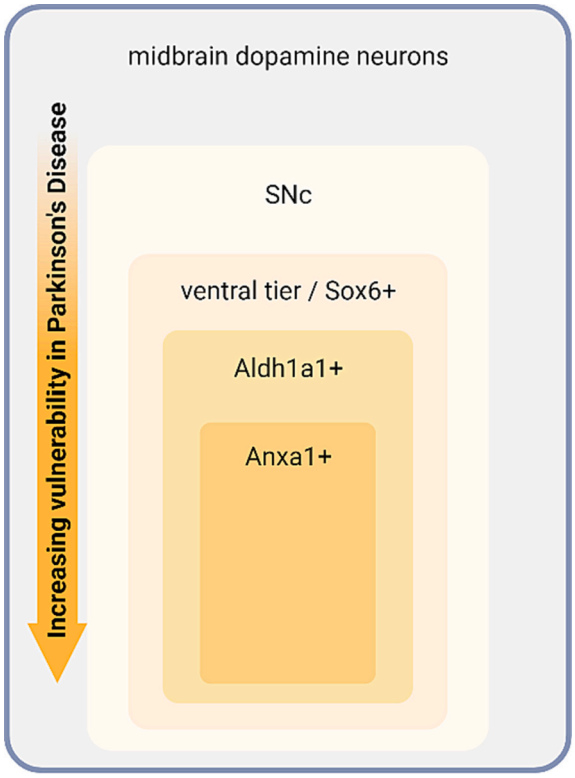

Fig. 1. Molecular Identities of dopamine neurons and their proposed vulnerability to degeneration in Parkinson's disease, Not all midbrain dopamine neurons are equally susceptible to degeneration in Parkinson's Disease. SNc dopamine neurons are more vulnerable than VTA dopamine neurons. Within the SNc there are again more vulnerable subsets that have been identified. The ventral tier of the SNc, which can be marked by expression of Sox6, is known to be vulnerable. Within this population, Aldh1a1+ dopamine neurons are vulnerable. A subpopulation within the Aldh1a1 population, marked by Anxa1, has recently been identified and linked to movement. It may be that this specific movement-sensitive population of dopamine neurons is the most vulnerable to degeneration in PD, although further testing and characterization are required. Increasing molecular specificity in defining vulnerable dopamine neuron populations in PD may be useful in early diagnosis and treatment.

dependent synaptic plasticity. Although the role of serotonergic neurons still remains somewhat unclear, release of dopamine from serotonergic terminals has been linked to the development of L-DOPA-induced dyskinesias in parkinsonian animals treated with levodopa (Carta et al., 2007; Rylander et al., 2010). Additionally, as dopamine neurons slowly degenerate, other adaptations in dopamine signaling machinery and downstream basal ganglia circuit function are likely to influence L-DOPA's efficacy.

The better we understand dopamine system function, both in the intact brain and in degenerative disease models, the better we will be able to develop therapeutics that restore healthy dopamine dynamics at different stages of disease progression. New approaches are required to address disease symptoms that are currently untouched, or even worsened, by dopamine replacement therapy, such as cognitive functions. Early intervention to restore natural dopamine dynamics might also slow disease progression or prolong the efficacy of dopaminergic treatment by preventing cellular, synaptic or circuit adaptations, including aberrant synaptic plasticity, which have been linked to complications such as levodopa-induced dyskinesia (Borgkvist et al., 2018; Picconi et al., 2003).

Here, we review recent conceptual advances in our basic understanding of the dopamine system with special attention to their import for PD. We summarize our understanding of dopamine circuitry across three axes: (1) molecular identity, (2) network identity, and (3) computational identity. We address how each of these identities may relate to PD and L-DOPA efficacy and provide thoughts on paths forward in PD-related dopamine research. Continued integration of dopamine-related basic and preclinical research will be important to stimulate breakthroughs in PD treatment.

2. Molecular identity

Historically, dopamine neurons have been identified by their expression of markers such tyrosine hydroxylase (TH), the rate-limiting enzyme for dopamine production, and by electrophysiological characteristics such as hyperpolarization-activated cation currents (I_h) and wide action potential waveforms (Grace and Bunney, 1983; Grace and Onn, 1989; Guyenet and Aghajanian, 1978; Pickel et al., 1977). More recently, it has become clear that these criteria for identifying dopamine neurons are not sufficient. For example, some dopamine neurons have minimal I_h and transgenic mouse lines based on the TH promoter can misidentify dopamine neurons (Lammel et al., 2008, 2015; Margolis et al., 2006). Moreover, single-cell sequencing experiments have made clear that subpopulations of dopamine neurons can be distinguished by other molecular markers such as Sox6, Aldh1a1, Anxa1, and VgluT2, with a remarkable degree of homology across species (Azcorra et al., 2023; Gaertner et al., 2022; Kamath et al., 2022; Poulin et al., 2020). In the healthy brain, it is likely that these molecularly-defined subpopulations of dopamine neurons have distinct functions in neural circuits (Azcorra et al., 2023), which will be important to consider in the context of PD (see Computational Identity section). Identifying molecular markers for subpopulations of dopamine neurons may also guide the way in terms of molecular drug targets directed at specific dopamine neuron subpopulations.

Molecular identity is likely related to vulnerability to degeneration (Fig. 1). Aldh1a1-expressing dopamine neurons are among the first to degenerate in PD (G. Liu et al., 2014; Poulin et al., 2014). These dopamine neurons are primarily located in the ventral tier of the substantia nigra pars compacta (SNc), which is expanded in primates relative to rodents (Double et al., 2010; Fu et al., 2016). Aldh1a1 encodes aldehyde dehydrogenase, which breaks down DOPAL, a neurotoxic metabolite of dopamine that causes aggregation of alpha-synuclein. Therefore, there is speculation that some problem in Aldh1a1+ expression or function allows for buildup of DOPAL and subsequent degeneration of the Aldh1a1+ population early in PD progression (Cai et al., 2014; Masato et al., 2023). Despite the fact that Aldh1a1+ dopamine neurons are particularly vulnerable to degeneration, ablating Aldh1a1+ dopamine neurons does *not* induce a parkinsonian motor phenotype, other than a small loss of high-velocity running (>20 cm/s; Wu et al., 2019). Instead, it results in a severe motor learning phenotype (an inability to improve on the accelerating rotarod task). Recently, a new subtype within the Aldh1a1+ population has been identified, which is characterized by the expression of Anxa1. The activity of Anxa1+ dopamine neurons is strikingly correlated with locomotion but not with reward (Azcorra et al., 2023). As yet, it remains unclear what the casual relationship of Anxa1+ dopamine neurons is with parkinsonian phenotypes, but given their location and encoding properties, a link is likely and should be further studied.

Not all ventral tier dopamine neurons are Anxa1/Aldh1a1+ dopamine neurons. After Aldh1a1+ dopamine neurons degenerate, other ventral tier dopamine neurons may follow. Sox6 is a molecular marker that more fully encompasses the ventral tier population (including but not limited to Aldh1a1+ dopamine neurons). Sox6+ dopamine neurons have been found to selectively degenerate in human PD patients (Kamath et al., 2022; Luppi et al., 2021). Ablating ventral tier dopamine neurons broadly using the marker Sox6, rather than Aldh1a1, may be more reflective of the profound loss of SNc dopamine neurons that accompanies symptomatic PD (Panman et al., 2014; Surmeier et al., 2017), but more investigation is necessary to confirm. On the other hand, the ablation of Aldh1a1+ (or even more specifically, Anxa1+) dopamine

neurons could model prodromal stages of PD. A more detailed understanding of the functions and symptoms that each molecularly-defined dopamine subpopulation corresponds to will be important for understanding PD staging. It will also be important for understanding which molecularly-based approaches to treatment are likely to be effective in PD patients depending on their individual disease progression. Interestingly, one study of SNc dopamine neurons in postmortem human tissue found that lower dopamine neuron cell counts were correlated with mild parkinsonian symptoms in neurological exams, even in people that had not been diagnosed with PD prior to death (Ross et al., 2004). Determining if Anxa1 is an important dopaminergic marker in humans and, if so, if the loss of the Anxa1+ dopamine neuron subpopulation is overrepresented in cases of early dopamine neuron loss in undiagnosed humans would be illuminating. Tying SNc dopaminergic cell loss in early PD to mechanisms of circuit dysfunction that might propel PD progression could be revealing.

While some molecular markers correspond to increased vulnerability in PD, others are related to neuroprotection. Vulnerable ventral tier Sox6+ dopamine neurons lack calbindin expression, for example. Calbindin-expressing dopamine neurons, including dopamine neurons located in the dorsal tier of SNc and in the ventral tegmental area (VTA), are relatively spared in PD (Damier et al., 1999; Kamath et al., 2022; Yamada et al., 1990). Calbindin may play a direct protective role by buffering calcium (Brimblecombe et al., 2019; Evans et al., 2017; Mongia et al., 2019; Surmeier and Schumacker, 2013). Another potential neuroprotective factor is VGLUT2. VGLUT2 is upregulated in response to neurotoxic insult, such as with MPTP and 6-OHDA, and alpha-synuclein stress (Kouwenhoven et al., 2020; Steinkellner et al., 2022). VGLUT2+ dopamine neurons (a subset of midbrain dopamine neurons located mainly in the ventral tegmental area (VTA) and substantia nigra pars lateralis (SNL)) are more resilient in both PD patients and animal models of PD, and conditional deletion of VGLUT2 in dopamine neurons leads to more degeneration in mouse models (Root et al., 2016; Steinkellner et al., 2022). A final example is Netrin-1, a protein involved in embryonic axon guidance. Netrin-1 has persistent expression in the SNc of adults that is significantly decreased in PD patients. In healthy conditions, netrin-1 prevents its receptor from triggering cell death (Mehlen et al., 1998). Therefore, downregulation of netrin-1 could be a cause of cell death. A conditional knockout of netrin-1 in dopamine neurons induces a parkinsonian phenotype in mice, while overexpression or pharmacological administration of this protein in mouse models of PD reduces parkinsonism and prevents dopamine cell loss (Jasmin et al., 2021; Livesey and Hunt, 1997). These molecular markers provide windows into neuroprotective mechanisms and how they may differ among dopamine neurons of different molecular subtypes. Adapting neuroprotective mechanisms for vulnerable dopamine neuron populations could be one effective therapeutic strategy if it can be implemented early in disease progression.

The molecular identities of dopamine neurons may also shape compensation during progressive neurodegeneration. When vulnerable molecularly-defined subpopulations of dopamine neurons (e.g. Aldh1a1+ dopamine neurons) slowly degenerate, do less vulnerable subpopulations of dopamine neurons compensate? If so, how? Do such compensatory mechanisms eventually become maladaptive, contributing to degeneration of dopamine neurons that survive the initial stages of PD? One potential form of compensation occurs at the anatomical level. When dopamine axons degenerate, surviving dopamine neurons can branch their axonal arbors and show pronounced hyperexcitability (Bishop et al., 2010; Chen et al., 2009). This axonal branching and increased excitability can help prevent striatal dopamine levels from dropping precipitously early in the disease and it may be a reason why a large percentage of dopamine neurons must degenerate before motor symptoms become evident and PD is diagnosed (Hornykiewicz and Kish, 1987; Kish et al., 1988). However, the extent of compensation in early PD, including signs that may emerge prior to diagnosis, is unclear.

Although evidence in humans is currently lacking, animal research shows that axonal branching of dopamine neurons is a potential mechanism for compensation. Work by Tanguay et al. (2021) showed extensive branching of surviving SNc dopamine neurons following neonatal 6-OHDA lesions. Sprouting in response to partial 6-OHDA lesions in adulthood can also occur, providing some recovery of striatal dopamine concentrations and associated motor behaviors (Bez et al., 2016; Blanchard et al., 1996; Deumens et al., 2002; Robinson and Whishaw, 1988). If this compensation via axonal branching and intrinsic firing is indeed occurring in PD, an important question is whether this form of compensation can occur across or only within molecular subtypes. Can a dopamine neuron of one molecular identity branch into the territory of a dopamine neuron from a different molecular identity? The answer to this question would provide important information about the relationship between molecular identities of dopamine neurons and PD staging.

Functional compensation may also occur in molecularly-defined dopamine neuron subpopulations. These may help increase dopamine release or amplify its impact on downstream circuit elements. Surviving dopamine neurons exhibit changes such as increased dopamine metabolism, reduced dopamine transporter (DAT) expression, and increased D2 receptors (summarized in Blesa et al., 2017), but more work is required to identify if these changes occur in specific molecular subtypes.

Finally, although the molecular identities of dopamine neurons are being discovered and well-characterized under healthy conditions, these identities may shift during degenerative processes. As gene expression patterns shift with degeneration, do we need to re-classify neurons? As noted above, VGLUT2 expression increases in response to insults to the dopamine system. When VGLUT2 expression increases, it may not only promote survival, but alter function, by increasing glutamate co-release (Steinkellner et al., 2022). Understanding how compensatory mechanisms during degeneration may effectively cause dopamine neurons to switch molecular subtypes (e.g. via switching to a more glutamatergic identity) will be important to understand as it may have effects on the computational identity of surviving neurons and therefore on the dopamine-dependent behaviors that are supported by the surviving aspects of the dopamine system.

3. Network identity

Subpopulations of dopamine neurons can be defined by molecular markers, but it is equally important to consider how subpopulations of dopamine neurons are embedded in neural circuits (“network identity”; Lerner et al., 2016). The network identities of dopamine neurons are related to their molecular identities (Poulin et al., 2018, 2020), but these relationships are not 1:1 and could change over the course of PD progression. Projection target-defined subpopulations of dopamine neurons have profoundly different physiology. For example, many medial VTA dopamine neurons projecting to the prefrontal cortex and nucleus accumbens medial shell lack I_h and have therefore been excluded from traditional studies of dopamine (Lammel et al., 2008). Meanwhile, dopamine neurons that project to the dorsolateral striatum (DLS), which are involved in motor functions and PD, have prominent I_h and higher tonic firing rates than other dopamine neurons (Farassat et al., 2019; Lerner et al., 2015).

Projection-defined dopamine neurons also have distinct global input connectivity motifs (Beier et al., 2015; Lerner et al., 2015; Menegas et al., 2015; Watabe-Uchida et al., 2012). SNc dopamine neurons, which project mainly to dorsal striatum, receive a much larger proportion of their inputs from inhibitory brain areas (such as the striatum, globus pallidus external segment, central amygdala, and bed nucleus of the stria terminalis) than VTA dopamine neurons, which project largely to ventral striatum. Within SNc-projecting populations, differences in input patterns between dopamine neurons projecting to the dorsomedial striatum, the dorsolateral striatum, and the caudal tail of the striatum can be distinguished (Lerner et al., 2015; Menegas et al., 2015). One

prominent way these differences manifest is in patterns of reciprocal connectivity between striatal subregions and the midbrain dopamine neurons that innervate them (Ambrosi and Lerner, 2022; Haber et al., 2000; Lerner et al., 2015).

In terms of outputs, although dopamine neurons are well-known for their highly complex axonal arborizations in striatum (Matsuda et al., 2009), projection-defined dopamine neurons also generally restrict their arbors within striatal subregions and do not display prominent collateralization (Beier et al., 2015; Lerner et al., 2015). This circuit organization is important as it implies that different subregions of the striatum can receive distinct dopamine signals generated by independently operating parallel circuits. Indeed, it has been overwhelmingly confirmed that dopamine signals vary by subregion during behavior (Cohen et al., 2012; Parker et al., 2016; Saunders et al., 2018; Seiler et al., 2022; Tian et al., 2016; van Elzelingen et al., 2022).

Network identities can be related to patterns of degeneration in PD. SNc dopamine neurons degenerate in a lateral to medial pattern, which corresponds to dopamine depletion beginning in DLS and progressing towards dorsomedial striatum (DMS; Nandhagopal et al., 2009). Since VTA dopamine neurons are spared until very late in disease, dopamine innervation of target areas like the nucleus accumbens and prefrontal cortex are relatively intact. However, patterns of degeneration are not necessarily the same as patterns of dysfunction. In many mouse models of PD, dopamine neurons display functional electrophysiological deficits even in the absence of or preceding degeneration. To name a few examples: dopamine neurons in MitoPark mice show decreased endogenous dopamine and a loss of pacemaking, alpha-synuclein overexpression reduces TH and AADC activity and impairs dopamine release, and PINK-1 deficient mice show hyperexcitability and irregular firing in SNc dopamine neurons (Bishop et al., 2010; Branch et al., 2016; Cramb et al., 2023; Lam et al., 2011; Venda et al., 2010). Symptom progression in PD may be related to patterns of dysfunction as much or even more so than patterns of degeneration. For example, although DLS-projecting dopamine neurons degenerate earlier in PD, the DLS is thought to be responsible for habitual motor actions, which become difficult primarily for late-stage PD patients (Torres et al., 2011; Yin et al., 2004, 2005). On the other hand, DMS-projecting dopamine neurons degenerate later in PD, but the role of DMS is primarily in flexible learning, a domain where difficulties are observed in early PD prior to classical motor impairments (Peterson et al., 2009; Swainson et al., 2000). Therefore, it is important to study dysfunction in surviving dopamine subpopulations in PD. Characterizing aberrant patterns of dopamine release in PD models might explain which PD symptoms are dopamine-dependent, but not treated effectively with L-DOPA, versus due to dysfunction of other brain systems. How dysfunction in subpopulations of surviving dopamine neurons in PD interacts with the function of downstream basal ganglia circuits will also be important to explore.

4. Computational identity

As might be expected from the distinct molecular and network identities of subpopulations of dopamine neurons, these subpopulations also differ in their "computational identities," i.e. in the types of information they encode. The concept of computational identity encompasses the idea that neuronal cell types can be usefully defined by their roles in information storage or processing to support the functioning of a complex circuit. Translating between molecular, network, and computational identities is important for communication between molecular/cellular and systems/computational scientists. Computational identity is a crucial factor to consider in the context of PD, where distinct computational functions of subpopulations of dopamine neurons may be lost at different times during disease progression, either due to outright degeneration or to dysfunction that disrupts normal activity patterns.

Dopamine neurons encode information through multiple timescales of firing. Dopamine neurons are tonically active, meaning they exhibit spontaneous pacemaker firing and create a continuously present concentration of dopamine in the brain (Grace and Bunney, 1983). Tonic dopamine activity is traditionally linked to motivation and movement (Freed and Yamamoto, 1985; Niv et al., 2007; Salamone and Correa, 2012). Dopamine neurons also show phasic activity patterns composed of fast, synchronous burst firing that are associated with learning and reward (Cohen et al., 2012; Phillips et al., 2003; Schultz, 2007). Some evidence in mice suggests that the efficacy of L-DOPA for motor symptoms of PD does not require phasic dopamine release (H. Liu et al., 2022b). However, the assignment of functions to tonic or phasic dopamine signaling may be a false dichotomy—in reality, there is likely more nuance to consider with vast implications for PD (Berke, 2018).

Classical work on the computational function of phasic dopamine has focused on reward prediction error (RPE), the difference between actual and expected reward (Schultz et al., 1997), although more recent work suggests that RPE is not the whole story (Bakhurin et al., 2023; Coddington et al., 2023; Jeong et al., 2022; Lerner et al., 2021). An RPE-encoding function for dopamine does not explain why dopamine depletion results in parkinsonism. A growing appreciation for the idea that there is heterogeneity in the encoding properties of dopamine neurons is relevant to resolving this conflict (Collins and Saunders, 2020; Engelhard et al., 2019; Lerner et al., 2021).

One way to test RPE encoding is by using optogenetic stimulation of dopamine neuron subpopulations to see if artificial prediction errors can be created. While optogenetic stimulation of both SNc and VTA dopamine neurons is reinforcing (i.e. able to support self-stimulation behavior), only stimulation of VTA dopamine neurons supports other functions associated with RPE. Stimulation of VTA dopamine neurons, but not SNc dopamine neurons, can "unblock" learning about cues that would not otherwise generate RPE (Keiflin et al., 2019). Stimulation of VTA dopamine neurons can also generate more distal predictions, encode motivation, and attribute incentive value in Pavlovian conditioning (Fraser et al., 2023; Keiflin et al., 2019; Saunders et al., 2018).

In vivo electrophysiology recordings of SNc dopamine neurons have shown that they have movement-related phasic firing patterns, inconsistent with classic roles of tonic and phasic dopamine (da Silva et al., 2018; Dodson et al., 2016). Of particular note for this review, Dodson et al. (2016) found movement-linked dopamine neuron firing patterns in the SNc disappeared in a mouse model of PD overexpressing alpha-synuclein. Recordings of DLS-projecting SNc dopamine neurons also reveal that location within the SNc (possibly related to the molecular identity of the dopamine neurons) is relevant, with DLS-projecting dopamine neurons in the lateral SNc exhibiting more "bursty" firing patterns than DLS-projecting dopamine neurons in the medial SNc (Farassat et al., 2019).

Recordings of downstream dopamine signals in the dorsal striatum are mixed in terms of reporting movement correlations vs reward responsiveness. Some have observed time-locked reward signaling in striatal dopamine recordings and changes in reward-seeking behavior in response to optogenetic stimulation of SNc dopamine axons in striatum (Lerner et al., 2015; Saunders et al., 2018; Seiler et al., 2022; Tsutsui-Kimura et al., 2020; van Elzelingen et al., 2022). Others have found striatal dopamine axon activity and signaling to be linked to movement, even in the absence of reward (Azcorra et al., 2023; Howe and Dombeck, 2016; Markowitz et al., 2023). Still others posit that SNc dopamine signaling is responsible for encoding "action prediction errors," the difference between an expected action and the action that was taken (Greenstreet et al., 2022). Individual SNc dopamine neurons might play a role multiple computational functions, or distinct subpopulations might encode separate functions. Many of the described studies use different methods to record SNc dopamine neuron cell bodies, dopamine axon terminals, and downstream striatal dopamine release, and the investigators may therefore be recording from or manipulating different subsets of neurons, perhaps related to their molecular or network identities (Azcorra et al., 2023; Lerner et al., 2015, 2016; Luppi et al., 2021).

Thinking through the lens of computational identity highlights gaps in our understanding. For example, how can we explain the result that ablating Aldh1a1+ dopamine neurons, which are known to degenerate early in PD and which seem to carry movement-related signals, does not cause an obvious PD phenotype? Perhaps, although this subpopulation displays movement-related activity (Azcorra et al., 2023), it could be using information about movement to encode aspects of action prediction or other learning-related errors, in keeping with the learning and memory deficits observed in prodromal PD patients (Pausch et al., 2016; Wu et al., 2019).

It is likely that dopamine neuron subpopulations of different molecular and network identities also have different computational identities. However, these computational identities may be complex, involving several different information processing functions. We speculate that multiple computational functions per dopamine neuron subpopulation could occur due to the many layers of regulation of dopamine release and timing in different cellular compartments. Shifts in the regulation of dopamine release could then alter computational identities in subpopulations of dopamine neurons before degeneration occurs in PD. One example arises when examining the local regulation of dopamine terminals in the striatum by acetylcholine. Recent work has shown that activation of nicotinic acetylcholine receptors on dopamine neuron terminals can evoke actional potentials independent of dopamine cell body activity (Kramer et al., 2022; C. Liu et al., 2022a). Although the importance of this mechanism for in vivo coordination of acetylcholine and dopamine signaling is as yet unclear (Krok et al., 2022; Matityahu et al., 2023), anticholinergics are the oldest class of drugs used to treat PD, so clarifying this relationship both at a synaptic level and as a computational mechanism will likely be fruitful for identifying paths forward in PD research.

Another example of the potential for multiple computational functions of dopamine neurons arises from the work of González-Rodríguez et al. (2021), who showed that motor function remains intact when dorsal striatal dopamine axons stop releasing dopamine. In this work, a mouse model of PD was generated in which mitochondrial complex I in dopamine neurons was disrupted (cNdufs2$^{-/-}$). cNdufs2$^{-/-}$mice exhibited Parkinsonism only later in the process of dopamine neuron degeneration when the somatodendritic release of dopamine in SNc was lost. Notably, the efficacy of L-DOPA in this progressive model varies with the stages of degeneration. Although associative learning was rescued by L-DOPA when striatal dopamine axons were intact (at P30), it could not be rescued later (at P60). Meanwhile, total movement in the open field could be rescued by L-DOPA far into the course of progressive degeneration (even up to P120).

The reasons for the changes in L-DOPA's efficacy in cNdufs2$^{-/-}$ mice over time are likely related to the different computational functions of dopamine for different behaviors. Associative learning depends critically on the timing of striatal dopamine release, which controls narrow windows for dopamine-dependent striatal synaptic plasticity (Yagishita et al., 2014). Cognitive deficits in prodromal PD could be due to subtle changes in striatal dopamine release resulting in suboptimal timing. In contrast, fine dopamine timing may be dispensable for gross motor function in the absence of learning requirements (Delignat-Lavaud et al., 2023). Mice that lack NMDA receptors in dopamine neurons (which are required for dopamine burst firing) have normal ambulation and rearing, explore normally, and can learn the accelerating rotarod task. However, dopamine neurons in these mice are hyporesponsive to reward, and the mice display reward learning deficits, including impaired habit formation (Wang et al., 2011; Zweifel et al., 2008). The dissociations observed in these dopamine-specific NMDA receptor KO mice help dissect which dopamine-dependent behaviors are dependent on phasic dopamine signaling as opposed to those likely enabled by dopamine tone alone. A caveat of these studies (Delignat-Lavaud et al., 2023; González-Rodríguez et al., 2021; Wang et al., 2011; Zweifel et al., 2008) and others is that the ability of neural circuits to compensate for the loss of dopamine may differ by developmental stage. Impressive compensation for the loss of dopamine can occur when dopamine reductions are performed in young mice (Castaneda et al., 1990; Golden et al., 2013; Moy, 1995; Moy et al., 1997; Schallert et al., 1989; Tanguay et al., 2021). By extension, it is possible there is also compensation for genetic alterations that change the function of dopamine neurons, such as the knockout of NMDA receptors or dopamine release machinery. Going forward, it will be important to consider whether mouse lines used in preclinical studies appropriately model PD progression in humans, which is both gradual and begins later in life.

Adaptations to the gradual loss of dopamine in adulthood may also differ by striatal subregion. For example, the different computational functions relayed by dopamine in each striatal subregion may have different requirements for phasic dopamine, as demonstrated by optogenetic stimulation of different projection-defined dopamine neurons (Seiler et al., 2022; Thorn et al., 2010; van der Merwe et al., 2023). This differing requirement for phasic signaling to drive behavioral changes could cause certain dopamine neurons to be more sensitive to dysfunction prior to degeneration, and could help explain why early cognitive deficits are more consistent with dysfunction in DMS-projecting dopamine neurons, despite their relative resistance to degeneration when compared to DLS-projecting neurons (Grospe et al., 2018).

As PD progresses, the computational identity of dopamine neurons may also be altered by decreased dopamine release, which has been seen in many mouse models of PD (see Cramb et al., 2023 for review). Diminishing dopamine signals in the dorsal striatum allows for other neurotransmitters, for example acetylcholine or serotonin, to exert larger effects on striatal function and plasticity. Imbalances in striatal neuromodulators in PD have been posited, but the exact time courses for the evolution of such imbalances are not fully understood. Over time, progressive changes could accumulate, causing cholinergic interneurons to exert an outsized effect on dopamine release and decoupling striatal dopamine release from cell body firing (Kramer et al., 2022; C. Liu et al., 2022a; McKinley et al., 2019; Rizzi and Tan, 2017; Ztaou and Amalric, 2019). Other changes, such as the change in dopamine-glutamate co-release mentioned above (Steinkellner et al., 2022), would be relevant to changes in computational identity as the striatum adapts to a lack of dopamine during PD progression. The release of dopamine and glutamate from the same population of VGLUT2+ dopamine neurons is proposed to relate to different aspects of behavior (Warlow et al., 2023), suggesting that upregulation of VGLUT2 in PD could cause a change in the computational function of VGLUT2+ dopamine neurons. Finally, dopamine neurons may use different timescales to transmit heterogenous information. For example, Markowitz et al. (2023) showed that DLS dopamine signals are related to different components of motor behavior when analyzed on a subsecond versus minutes-long timescale. This observation, in combination with theories of the role of dopamine in learning and the reinforcement of actions, rather than direct motor control, could help explain the long-duration response to L-DOPA in which some of the therapeutic effects of L-DOPA accumulate slowly over time and are experience-dependent (Anderson and Nutt, 2011; Beeler et al., 2010, 2012; Cheung et al., 2023). Interestingly, different effects of alpha-synuclein overexpression on dopamine release across timescales (facilitation on short timescales, depression on long timescales) have been observed and may suggest a mechanism by which the accumulation of alpha-synuclein could lead to distinct types of dysfunctional dopamine signaling on different timescales relevant to behavior (Somayaji et al., 2020). Theories of dopamine-dependent plasticity and motor learning may also be relevant in explaining why chronic L-DOPA treatment can lead to the excessive, involuntary movements known as L-DOPA-induced dyskinesias, if inappropriate motor behaviors are reinforced by mispatterned dopamine release.

5. Considerations for Parkinson's disease research going forward

The past decade has been a new renaissance for basic dopamine

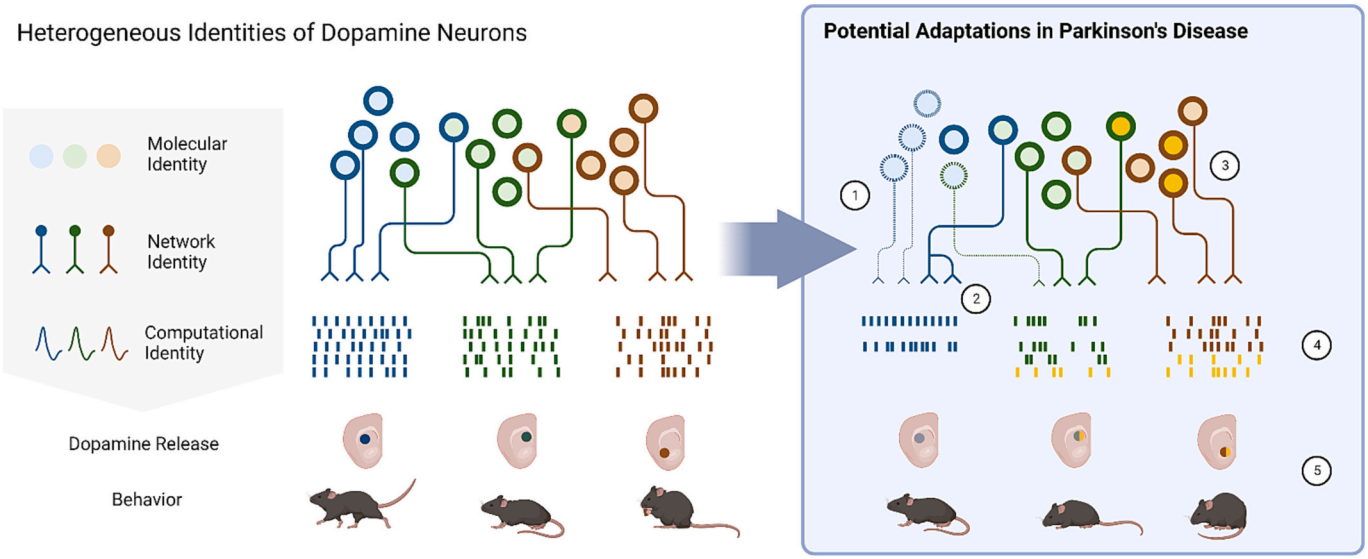

Fig. 2. Potential adaptions of heterogeneous dopamine neuron subpopulations during Parkinson's Disease progression. Dopamine neuron subpopulations can be defined in several ways – by molecular identity (patterns of gene expression), network identity (input and output connectivity motifs), and computational identity (information encoded). To understand Parkinson's Disease (PD) progression, it will be important to interface knowledge of these dopamine neuron identities with information about patterns of neurodegeneration and dysfunction across PD progression. Some potential changes in PD include: (1) selective vulnerability of particular molecular subpopulations of dopamine neurons (e.g. Aldh1a1+ dopamine neurons; blue) to degeneration (depicted as dashed outlined cells), (2) compensation by axonal sprouting of surviving dopamine neurons with the same network identity, which could increase dopamine in an affected downstream striatal subregion, but change local patterns of release, (3) changes in gene expression affecting molecular identity (e.g. upregulation of protective molecular factors like VGLUT2, shown as maroon cells turning yellow), (4) changes in the molecular and network identities of dopamine neurons could, in isolation or together, lead to changes in computational identity by altering firing patterns (shown as changes in raster plots) and/or neurotransmitter release properties (shown as spikes in raster turning yellow, e.g. representing an increase in glutamate release in the case of VGLUT2 upregulation), (5) in response to changes 1–4, downstream striatal circuit function and behavior will be altered. For example, the blue neurons may encode high speed movement initiations in control mice but fail to evoke movements in PD models. The red neurons could normally be motivating reward-seeking behavior but fail to do so in PD models, with implications for co-morbid depression. These are examples illustrating how the multiple identities of heterogeneous populations of dopamine neuron subpopulations could change during PD, but they are currently speculative and not an exhaustive list of potential adaptions. Adaptions occurring in PD at multiple levels of dopamine neuron identity will continue to evolve as the disease progresses. Understanding how complex interactions of identities influence circuit function across PD progression and, potentially, contribute to further disease progression will advance the field and provide inspiration for new interventions to alter the disease course. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

research. We now have precise genetic and circuit tracing tools for differentiating dopamine neuron subpopulations, and improved imaging and detection methods for monitoring fast in vivo release dynamics (Armand et al., 2021; Callaway and Luo, 2015; Ciabatti et al., 2017; Day-Cooney et al., 2022; Lerner et al., 2016; Sofroniew et al., 2016). Clever behavioral and computational work has also led to a much more sophisticated understanding of the computational functions of the intact dopamine system (Bassett and Sporns, 2017; Engelhard et al., 2019; Isik and Unal, 2023; Kennedy, 2022; Lerner et al., 2021). These new technical and conceptual approaches should be integrated by PD researchers as we work in parallel to develop creative new therapeutics addressing specific timescales of dopamine signaling or target distinct dopamine cell types.

Understanding dopamine system dysfunction in PD will require grappling with the complex identities of dopamine neurons (Fig. 2). We must interface the identities described here – molecular, network, and computational – to gain a comprehensive view of dopamine system dysfunction in PD. We now understand clearly that PD is a disorder of both dopamine system dysfunction *and* degeneration, causing both motor and non-motor symptoms. To understand the full course of PD progression, it is imperative to understand the evolving relationships between dysfunction and degeneration that produce changes in symptoms and treatment responsiveness over time. Elucidating the dopamine system dysfunctions that are left unaddressed by L-DOPA, the current standard of care, will guide the development of improved treatments. Finally, better characterizing the dysfunctions occurring in prodromal PD will allow earlier interventions that could prevent progression.

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CRediT authorship contribution statement

Jillian L. Seiler: Conceptualization, Writing – original draft, Writing – review & editing. **Xiaowen Zhuang:** Writing – review & editing. **Alexandra B. Nelson:** Conceptualization, Writing – review & editing, Funding acquisition. **Talia N. Lerner:** Conceptualization, Funding acquisition, Writing – original draft, Writing – review & editing.

Declaration of competing interest

None.

Data availability

No data was used for the research described in the article.

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References

Ambrosi, P., Lerner, T.N., 2022. Striatonigrostriatal circuit architecture for disinhibition of dopamine signaling. Cell Rep. 40 (7) https://doi.org/10.1016/j.celrep.2022.111228.

Anderson, E., Nutt, J., 2011. The long-duration response to levodopa: phenomenology, potential mechanisms and clinical implications. Parkinsonism Relat. Disord. 17 (8), 587–592. https://doi.org/10.1016/j.parkreldis.2011.03.014.

Arai, R., Karasawa, N., Nagatsu, I., 1996. Aromatic L-amino acid decarboxylase is present in serotonergic fibers of the striatum of the rat. A double-labeling immunofluorescence study. Brain Res. 706 (1), 177–179. https://doi.org/10.1016/0006-8993(95)01281-8.

Armand, E.J., Li, J., Xie, F., Luo, C., Mukamel, E.A., 2021. Single-cell sequencing of brain cell transcriptomes and epigenomes. Neuron 109 (1), 11–26. https://doi.org/10.1016/j.neuron.2020.12.010.

Azcorra, M., Gaertner, Z., Davidson, C., He, Q., Kim, H., Nagappan, S., Hayes, C.K., Ramakrishnan, C., Fenno, L., Kim, Y.S., Deisseroth, K., Longnecker, R., Awatramani, R., Dombeck, D.A., 2023. Unique functional responses differentially map onto genetic subtypes of dopamine neurons. Nat. Neurosci. 1–13 https://doi.org/10.1038/s41593-023-01401-9.

Bakhurin, K., Hughes, R.N., Jiang, Q., Fallon, I.P., Yin, H.H., 2023. *Force tuning explains changes in phasic dopamine signaling during stimulus-reward learning* (p. 2023.04.23.537994). bioRxiv. https://doi.org/10.1101/2023.04.23.537994.

Bassett, D.S., Sporns, O., 2017. Network neuroscience. Nat. Neurosci. 20 (3), 353–364. https://doi.org/10.1038/nn.4502.

Beeler, J.A., Cao, Z.F.H., Kheirbek, M.A., Ding, Y., Koranda, J., Murakami, M., Kang, U. J., Zhuang, X., 2010. Dopamine-dependent motor learning insight into levodopa's long-duration response. Ann. Neurol. 67 (5), 639–647. Scopus. https://doi.org/10.1002/ana.21947.

Beeler, J.A., Frank, M.J., McDaid, J., Alexander, E., Turkson, S., Sol Bernandez, M., McGehee, D.S., Zhuang, X., 2012. A role for dopamine-mediated learning in the pathophysiology and treatment of Parkinson's disease. Cell Rep. 2 (6), 1747–1761. https://doi.org/10.1016/j.celrep.2012.11.014.

Beier, K.T., Steinberg, E.E., DeLoach, K.E., Xie, S., Miyamichi, K., Schwarz, L., Gao, X.J., Kremer, E.J., Malenka, R.C., Luo, L., 2015. Circuit architecture of VTA dopamine neurons revealed by systematic Input–Output mapping. Cell 162 (3), 622–634. https://doi.org/10.1016/j.cell.2015.07.015.

Berke, J.D., 2018. What does dopamine mean? Nat. Neurosci. 21 (6), 787–793. https://doi.org/10.1038/s41593-018-0152-y.

Bez, F., Francardo, V., Cenci, M.A., 2016. Dramatic differences in susceptibility to l-DOPA-induced dyskinesia between mice that are aged before or after a nigrostriatal dopamine lesion. Neurobiol. Dis. 94, 213–225. https://doi.org/10.1016/j.nbd.2016.06.005.

Bishop, M.W., Chakraborty, S., Matthews, G.A.C., Dougalis, A., Wood, N.W., Festenstein, R., Ungless, M.A., 2010. Hyperexcitable substantia Nigra dopamine neurons in PINK1- and HtrA2/Omi-deficient mice. J. Neurophysiol. 104 (6), 3009–3020. https://doi.org/10.1152/jn.00466.2010.

Blanchard, V., Anglade, P., Dziewczapolski, G., Savasta, M., Agid, Y., Raisman-Vozari, R., 1996. Dopaminergic sprouting in the rat striatum after partial lesion of the substantia nigra. Brain Res. 709 (2), 319–325. https://doi.org/10.1016/0006-8993(95)01391-1.

Blesa, J., Trigo-Damas, I., Dileone, M., Del Rey, N.L.-G., Hernandez, L.F., Obeso, J.A., 2017. Compensatory mechanisms in Parkinson's disease: circuits adaptations and role in disease modification. Exp. Neurol. 298 (Pt B), 148–161. https://doi.org/10.1016/j.expneurol.2017.10.002.

Borgkvist, A., Lieberman, O.J., Sulzer, D., 2018. Synaptic plasticity may underlie l-DOPA induced dyskinesia. Curr. Opin. Neurobiol. 48, 71–78. https://doi.org/10.1016/j.conb.2017.10.021.

Branch, S.Y., Chen, C., Sharma, R., Lechleiter, J.D., Li, S., Beckstead, M.J., 2016. Dopaminergic neurons exhibit an age-dependent decline in electrophysiological parameters in the MitoPark mouse model of Parkinson's disease. J. Neurosci. 36 (14), 4026–4037. https://doi.org/10.1523/JNEUROSCI.1395-15.2016.

Brimblecombe, K.R., Vietti-Michelina, S., Platt, N.J., Kastli, R., Hnieno, A., Gracie, C.J., Cragg, S.J., 2019. Calbindin-D28K limits dopamine release in ventral but not dorsal striatum by regulating Ca2+ availability and dopamine transporter function. ACS Chem. Neurosci. 10 (8), 3419–3426. https://doi.org/10.1021/acschemneuro.9b00325.

Cai, H., Liu, G., Sun, L., Ding, J., 2014. Aldehyde dehydrogenase 1 making molecular inroads into the differential vulnerability of nigrostriatal dopaminergic neuron subtypes in Parkinson's disease. Translat. Neurodegener. 3, 27. https://doi.org/10.1186/2047-9158-3-27.

Callaway, E.M., Luo, L., 2015. Monosynaptic circuit tracing with glycoprotein-deleted rabies viruses. J. Neurosci. 35 (24), 8979–8985. https://doi.org/10.1523/JNEUROSCI.0409-15.2015.

Carta, M., Carlsson, T., Kirik, D., Björklund, A., 2007. Dopamine released from 5-HT terminals is the cause of L-DOPA-induced dyskinesia in parkinsonian rats. Brain: A J. Neurol. 130 (Pt 7), 1819–1833. https://doi.org/10.1093/brain/awm082.

Castaneda, E., Whishaw, I.Q., Lermer, L., Robinson, T.E., 1990. Dopamine depletion in neonatal rats: effects on behavior and striatal dopamine release assessed by intracerebral microdialysis during adulthood. Brain Res. 508 (1), 30–39. https://doi.org/10.1016/0006-8993(90)91113-U.

Chen, L., Zhang, Q.J., Liu, J., Wang, S., Ali, U., Gui, Z.H., Wang, Y., 2009. Chronic, systemic treatment with a metabotropic glutamate receptor 5 antagonist in 6-hydroxydopamine partially lesioned rats reverses abnormal firing of dopaminergic neurons. Brain Res. 1286, 192–200. https://doi.org/10.1016/j.brainres.2009.06.040.

Cheung, T.H.C., Ding, Y., Zhuang, X., Kang, U.J., 2023. Learning critically drives parkinsonian motor deficits through imbalanced striatal pathway recruitment. Proc. Natl. Acad. Sci. 120 (12), e2213093120 https://doi.org/10.1073/pnas.2213093120.

Ciabatti, E., González-Rueda, A., Mariotti, L., Morgese, F., Tripodi, M., 2017. Life-long genetic and functional access to neural circuits using self-inactivating rabies virus. Cell 170 (2), 382–392.e14. https://doi.org/10.1016/j.cell.2017.06.014.

Coddington, L.T., Lindo, S.E., Dudman, J.T., 2023. Mesolimbic dopamine adapts the rate of learning from action. Nature 1–9. https://doi.org/10.1038/s41586-022-05614-z.

Cohen, J.Y., Haesler, S., Vong, L., Lowell, B.B., Uchida, N., 2012. Neuron-type-specific signals for reward and punishment in the ventral tegmental area. Nature 482 (7383), 85–88. https://doi.org/10.1038/nature10754.

Collins, A.L., Saunders, B.T., 2020. Heterogeneity in striatal dopamine circuits: form and function in dynamic reward seeking. J. Neurosci. Res. 98 (6), 1046–1069. https://doi.org/10.1002/jnr.24587.

Cramb, K.M.L., Beccano-Kelly, D., Cragg, S.J., Wade-Martins, R., 2023. Impaired dopamine release in Parkinson's disease. Brain. https://doi.org/10.1093/brain/awad064 awad064.

Damier, P., Hirsch, E.C., Agid, Y., Graybiel, A.M., 1999. The substantia nigra of the human brain. II. Patterns of loss of dopamine-containing neurons in Parkinson's disease. Brain: A J. Neurol. 122 (Pt 8), 1437–1448. https://doi.org/10.1093/brain/122.8.1437.

Day-Cooney, J., Dalangin, R., Zhong, H., Mao, T., 2022. Genetically encoded fluorescent sensors for imaging neuronal dynamics in vivo. J. Neurochem. https://doi.org/10.1111/jnc.15608. *n/a*(n/a).

Delignat-Lavaud, B., Kano, J., Ducrot, C., Massé, I., Mukherjee, S., Giguère, N., Moquin, L., Lévesque, C., Burke, S., Denis, R., Bourque, M.-J., Tchung, A., Rosa-Neto, P., Lévesque, D., De Beaumont, L., Trudeau, L.-É., 2023. Synaptotagmin-1-dependent phasic axonal dopamine release is dispensable for basic motor behaviors in mice. Nat. Commun. 14 (1), Article 1. https://doi.org/10.1038/s41467-023-39805-7.

Deumens, R., Blokland, A., Prickaerts, J., 2002. Modeling Parkinson's disease in rats: an evaluation of 6-OHDA lesions of the nigrostriatal pathway. Exp. Neurol. 175 (2), 303–317. https://doi.org/10.1006/exnr.2002.7891.

Dodson, P.D., Dreyer, J.K., Jennings, K.A., Syed, E.C.J., Wade-Martins, R., Cragg, S.J., Bolam, J.P., Magill, P.J., 2016. Representation of spontaneous movement by dopaminergic neurons is cell-type selective and disrupted in parkinsonism. Proc. Natl. Acad. Sci. U. S. A. 113 (15), E2180–E2188. https://doi.org/10.1073/pnas.1515941113.

Double, K.L., Reyes, S., Werry, E.L., Halliday, G.M., 2010. Selective cell death in neurodegeneration: why are some neurons spared in vulnerable regions? Prog. Neurobiol. 92 (3), 316–329. https://doi.org/10.1016/j.pneurobio.2010.06.001.

van Elzelingen, W., Warnaar, P., Matos, J., Bastet, W., Jonkman, R., Smulders, D., Goedhoop, J., Denys, D., Arbab, T., Willuhn, I., 2022. Striatal dopamine signals are region specific and temporally stable across action-sequence habit formation. Curr. Biol. 32 (5), 1163–1174.e6. https://doi.org/10.1016/j.cub.2021.12.027.

Engelhard, B., Finkelstein, J., Cox, J., Fleming, W., Jang, H.J., Ornelas, S., Koay, S.A., Thiberge, S.Y., Daw, N.D., Tank, D.W., Witten, I.B., 2019. Specialized coding of sensory, motor and cognitive variables in VTA dopamine neurons. Nature 570 (7762). https://doi.org/10.1038/s41586-019-1261-9. Article 7762.

Evans, R.C., Zhu, M., Khaliq, Z.M., 2017. Dopamine inhibition differentially controls excitability of substantia Nigra dopamine neuron subpopulations through T-type calcium channels. J. Neurosci. 37 (13), 3704–3720. https://doi.org/10.1523/JNEUROSCI.0117-17.2017.

Farassat, N., Costa, K.M., Stojanovic, S., Albert, S., Kovacheva, L., Shin, J., Egger, R., Somayaji, M., Duvarci, S., Schneider, G., Roeper, J., 2019. In vivo functional diversity of midbrain dopamine neurons within identified axonal projections. eLife 8, e48408. https://doi.org/10.7554/eLife.48408.

Fraser, K.M., Pribut, H.J., Janak, P.H., Keiflin, R., 2023. From prediction to action: dissociable roles of ventral tegmental area and substantia Nigra dopamine neurons in instrumental reinforcement. J. Neurosci. Off. J. Soc. Neurosci. 43 (21), 3895–3908. https://doi.org/10.1523/JNEUROSCI.0028-23.2023.

Freed, C.R., Yamamoto, B.K., 1985. Regional brain dopamine metabolism: a marker for the speed, direction, and posture of moving animals. Science 229 (4708), 62–65. https://doi.org/10.1126/science.4012312.

Fu, Y., Paxinos, G., Watson, C., Halliday, G.M., 2016. The substantia nigra and ventral tegmental dopaminergic neurons from development to degeneration. J. Chem. Neuroanat. 76, 98–107. https://doi.org/10.1016/j.jchemneu.2016.02.001.

Gaertner, Z., Azcorra, M., Dombeck, D.A., Awatramani, R., 2022. Molecular heterogeneity in the substantia nigra: a roadmap for understanding PD motor pathophysiology. Neurobiol. Dis. 175, 105925 https://doi.org/10.1016/j.nbd.2022.105925.

Golden, J.P., Demaro, J.A., Knoten, A., Hoshi, M., Pehek, E., Johnson, E.M., Gereau, R. W., Jain, S., 2013. Dopamine-dependent compensation maintains motor behavior in mice with developmental ablation of dopaminergic neurons. J. Neurosci. 33 (43), 17095–17107. https://doi.org/10.1523/JNEUROSCI.0890-13.2013.

González-Rodríguez, P., Zampese, E., Stout, K.A., Guzman, J.N., Ilijic, E., Yang, B., Tkatch, T., Stavarache, M.A., Wokosin, D.L., Gao, L., Kaplitt, M.G., López-Barneo, J., Schumacker, P.T., Surmeier, D.J., 2021. Disruption of mitochondrial complex I

induces progressive parkinsonism. Nature 599 (7886), 650–656. https://doi.org/10.1038/s41586-021-04059-0.
Grace, A.A., Bunney, B.S., 1983. Intracellular and extracellular electrophysiology of nigral dopaminergic neurons—1. Identification and characterization. Neuroscience 10 (2), 301–315. https://doi.org/10.1016/0306-4522(83)90135-5.
Grace, A.A., Onn, S.P., 1989. Morphology and electrophysiological properties of immunocytochemically identified rat dopamine neurons recorded in vitro. J. Neurosci. 9 (10), 3463–3481. https://doi.org/10.1523/JNEUROSCI.09-10-03463.1989.
Greenstreet, F., Vergara, H.M., Pati, S., Schwarz, L., Wisdom, M., Marbach, F., Johansson, Y., Rollik, L., Moskovitz, T., Clopath, C., Stephenson-Jones, M., 2022. Action prediction error: a value-free dopaminergic teaching signal that drives stable learning (p. 2022.09.12.507572). bioRxiv. https://doi.org/10.1101/2022.09.12.507572.
Grospe, G.M., Baker, P.M., Ragozzino, M.E., 2018. Cognitive flexibility deficits following 6-OHDA lesions of the rat dorsomedial striatum. Neuroscience 374, 80–90. https://doi.org/10.1016/j.neuroscience.2018.01.032.
Guyenet, P.G., Aghajanian, G.K., 1978. Antidromic identification of dopaminergic and other output neurons of the rat substantia nigra. Brain Res. 150 (1), 69–84. https://doi.org/10.1016/0006-8993(78)90654-6.
Haber, S.N., Fudge, J.L., McFarland, N.R., 2000. Striatonigrostriatal pathways in Primates form an ascending spiral from the Shell to the dorsolateral striatum. J. Neurosci. 20 (6), 2369–2382. https://doi.org/10.1523/JNEUROSCI.20-06-02369.2000.
Hornykiewicz, O., Kish, S.J., 1987. Biochemical pathophysiology of Parkinson's disease. Adv. Neurol. 45, 19–34.
Howe, M.W., Dombeck, D.A., 2016. Rapid signalling in distinct dopaminergic axons during locomotion and reward. Nature 535 (7613), 505–510. https://doi.org/10.1038/nature18942.
Isik, S., Unal, G., 2023. Open-source software for automated rodent behavioral analysis. Front. Neurosci. 17, 1149027. https://doi.org/10.3389/fnins.2023.1149027.
Jasmin, M., Ahn, E.H., Voutilainen, M.H., Fombonne, J., Guix, C., Viljakainen, T., Kang, S.S., Yu, L., Saarma, M., Mehlen, P., Ye, K., 2021. Netrin-1 and its receptor DCC modulate survival and death of dopamine neurons and Parkinson's disease features. EMBO J. 40 (3), e105537 https://doi.org/10.15252/embj.2020105537.
Jeong, H., Taylor, A., Floeder, J.R., Lohmann, M., Mihalas, S., Wu, B., Zhou, M., Burke, D.A., Namboodiri, V.M.K., 2022. Mesolimbic dopamine release conveys causal associations. Science eabq6740. https://doi.org/10.1126/science.abq6740.
Kamath, T., Abdulraouf, A., Burris, S.J., Langlieb, J., Gazestani, V., Nadaf, N.M., Balderrama, K., Vanderburg, C., Macosko, E.Z., 2022. Single-cell genomic profiling of human dopamine neurons identifies a population that selectively degenerates in Parkinson's disease. Nat. Neurosci. 25 (5) https://doi.org/10.1038/s41593-022-01061-1. Article 5.
Keiflin, R., Pribut, H.J., Shah, N.B., Janak, P.H., 2019. Ventral tegmental dopamine neurons participate in reward identity predictions. Curr. Biol. 29 (1), 93–103.e3. https://doi.org/10.1016/j.cub.2018.11.050.
Kennedy, A., 2022. The what, how, and why of naturalistic behavior. Curr. Opin. Neurobiol. 74, 102549 https://doi.org/10.1016/j.conb.2022.102549.
Kish, S.J., Shannak, K., Hornykiewicz, O., 1988. Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. N. Engl. J. Med. 318 (14), 876–880. https://doi.org/10.1056/NEJM198804073181402.
Kitahama, K., Denoyer, M., Raynaud, B., Borri-Voltattorni, C., Weber, M., Jouvet, M., 1990. Aromatic L-amino acid decarboxylase-immunohistochemistry in the cat lower brainstem and midbrain. J. Comp. Neurol. 302 (4), 935–953. https://doi.org/10.1002/cne.903020418.
Kouwenhoven, W.M., Fortin, G., Penttinen, A.-M., Florence, C., Delignat-Lavaud, B., Bourque, M.-J., Trimbuch, T., Luppi, M.P., Salvail-Lacoste, A., Legault, P., Poulin, J.-F., Rosenmund, C., Awatramani, R., Trudeau, L.-É., 2020. VGluT2 expression in dopamine neurons contributes to Postlesional striatal Reinnervation. J. Neurosci. 40 (43), 8262–8275. https://doi.org/10.1523/JNEUROSCI.0823-20.2020.
Kramer, P.F., Brill-Weil, S.G., Cummins, A.C., Zhang, R., Camacho-Hernandez, G.A., Newman, A.H., Eldridge, M.A.G., Averbeck, B.B., Khaliq, Z.M., 2022. Synaptic-like axo-axonal transmission from striatal cholinergic interneurons onto dopaminergic fibers. Neuron 110 (18), 2949–2960.e4. https://doi.org/10.1016/j.neuron.2022.07.011.
Krok, A.C., Mistry, P., Li, Y., Tritsch, N.X., 2022. Intrinsic reward-like dopamine and acetylcholine dynamics in striatum (p. 2022.09.09.507300). bioRxiv. https://doi.org/10.1101/2022.09.09.507300.
Lam, H.A., Wu, N., Cely, I., Kelly, R.L., Hean, S., Richter, F., Magen, I., Cepeda, C., Ackerson, L.C., Walwyn, W., Masliah, E., Chesselet, M.F., Levine, M.S., Maidment, N. T., 2011. Elevated tonic extracellular dopamine concentration and altered dopamine modulation of synaptic activity precede dopamine loss in the striatum of mice overexpressing human α-synuclein. J. Neurosci. Res. 89 (7), 1091–1102. https://doi.org/10.1002/JNR.22611.
Lammel, S., Hetzel, A., Häckel, O., Jones, I., Liss, B., Roeper, J., 2008. Unique properties of Mesoprefrontal neurons within a dual Mesocorticolimbic dopamine system. Neuron 57 (5), 760–773. https://doi.org/10.1016/j.neuron.2008.01.022.
Lammel, S., Steinberg, E.E., Földy, C., Wall, N.R., Beier, K., Luo, L., Malenka, R.C., 2015. Diversity of transgenic mouse models for selective targeting of midbrain dopamine neurons. Neuron 85 (2), 429–438. https://doi.org/10.1016/j.neuron.2014.12.036.
Lerner, T.N., Shilyansky, C., Davidson, T.J., Evans, K.E., Beier, K.T., Zalocusky, K.A., Crow, A.K., Malenka, R.C., Luo, L., Tomer, R., Deisseroth, K., 2015. Intact-brain analyses reveal distinct information carried by SNc dopamine subcircuits. Cell 162 (3), 635–647. https://doi.org/10.1016/j.cell.2015.07.014.
Lerner, T.N., Ye, L., Deisseroth, K., 2016. Communication in neural circuits: tools, opportunities, and challenges. Cell 164 (6), 1136–1150. https://doi.org/10.1016/j.cell.2016.02.027.
Lerner, T.N., Holloway, A.L., Seiler, J.L., 2021. Dopamine, updated: reward prediction error and beyond. Curr. Opin. Neurobiol. 67, 123–130. https://doi.org/10.1016/j.conb.2020.10.012.
Liu, C., Cai, X., Ritzau-Jost, A., Kramer, P.F., Li, Y., Khaliq, Z.M., Hallermann, S., Kaeser, P.S., 2022a. An Action Potential Initiation mechanism in Distal Axons for the Control of Dopamine Release, p. 8.
Liu, G., Yu, J., Ding, J., Xie, C., Sun, L., Rudenko, I., Zheng, W., Sastry, N., Luo, J., Rudow, G., Troncoso, J.C., Cai, H., 2014. Aldehyde dehydrogenase 1 defines and protects a nigrostriatal dopaminergic neuron subpopulation. J. Clin. Invest. 124 (7), 3032–3046. https://doi.org/10.1172/JCI72176.
Liu, H., Melani, R., Sankaramanchi, A., Zeng, R., Maltese, M., Martin, J.R., Tritsch, N.X., 2022b. A permissive role for dopamine in the production of vigorous movements (p. 2022.11.03.514328). bioRxiv. https://doi.org/10.1101/2022.11.03.514328.
Livesey, F.J., Hunt, S.P., 1997. Netrin and netrin receptor expression in the embryonic mammalian nervous system suggests roles in retinal, striatal, nigral, and cerebellar development. Mol. Cell. Neurosci. 8 (6), 417–429. https://doi.org/10.1006/mcne.1997.0598.
Luppi, M.P., Azcorra, M., Caronia-Brown, G., Poulin, J.-F., Gaertner, Z., Gatica, S., Moreno-Ramos, O.A., Nouri, N., Dubois, M., Ma, Y.C., Ramakrishnan, C., Fenno, L., Kim, Y.S., Deisseroth, K., Cicchetti, F., Dombeck, D.A., Awatramani, R., 2021. Sox6 expression distinguishes dorsally and ventrally biased dopamine neurons in the substantia nigra with distinctive properties and embryonic origins. Cell Rep. 37 (6) https://doi.org/10.1016/j.celrep.2021.109975.
Maeda, T., Nagata, K., Yoshida, Y., Kannari, K., 2005. Serotonergic hyperinnervation into the dopaminergic denervated striatum compensates for dopamine conversion from exogenously administered l-DOPA. Brain Res. 1046 (1–2), 230–233. https://doi.org/10.1016/j.brainres.2005.04.019.
Margolis, E.B., Lock, H., Hjelmstad, G.O., Fields, H.L., 2006. The ventral tegmental area revisited: is there an electrophysiological marker for dopaminergic neurons? J. Physiol. 577 (3), 907–924. https://doi.org/10.1113/jphysiol.2006.117069.
Markowitz, J.E., Gillis, W.F., Jay, M., Wood, J., Harris, R.W., Cieszkowski, R., Scott, R., Brann, D., Koveal, D., Kula, T., Weinreb, C., Osman, M.A.M., Pinto, S.R., Uchida, N., Linderman, S.W., Sabatini, B.L., Datta, S.R., 2023. Spontaneous behaviour is structured by reinforcement without explicit reward. Nature 614 (7946), 108–117. https://doi.org/10.1038/s41586-022-05611-2.
Masato, A., Plotegher, N., Terrin, F., Sandre, M., Faustini, G., Thor, A., Adams, S., Berti, G., Cogo, S., De Lazzari, F., Fontana, C.M., Martinez, P.A., Strong, R., Bandopadhyay, R., Bisaglia, M., Bellucci, A., Greggio, E., Dalla Valle, L., Boassa, D., Bubacco, L., 2023. DOPAL initiates αSynuclein-dependent impaired proteostasis and degeneration of neuronal projections in Parkinson's disease. Npj Parkinson's Disease 9 (1). https://doi.org/10.1038/s41531-023-00485-1. Article 1.
Matityahu, L., Gilin, N., Sarpong, G.A., Atamna, Y., Tiroshi, L., Tritsch, N.X., Wickens, J. R., Goldberg, J.A., 2023. Acetylcholine waves and dopamine release in the striatum. Nat. Commun. 14 (1) https://doi.org/10.1038/s41467-023-42311-5. Article 1.
Matsuda, W., Furuta, T., Nakamura, K.C., Hioki, H., Fujiyama, F., Arai, R., Kaneko, T., 2009. Single nigrostriatal dopaminergic neurons form widely spread and highly dense axonal Arborizations in the Neostriatum. J. Neurosci. 29 (2), 444–453. https://doi.org/10.1523/JNEUROSCI.4029-08.2009.
McKinley, J.W., Shi, Z., Kawikova, I., Hur, M., Bamford, I.J., Sudarsana Devi, S.P., Vahedipour, A., Darvas, M., Bamford, N.S., 2019. Dopamine deficiency reduces striatal cholinergic interneuron function in models of Parkinson's disease. Neuron 103 (6), 1056–1072.e6. https://doi.org/10.1016/j.neuron.2019.06.013.
Mehlen, P., Rabizadeh, S., Snipas, S.J., Assa-Munt, N., Salvesen, G.S., Bredesen, D.E., 1998. The DCC gene product induces apoptosis by a mechanism requiring receptor proteolysis. Nature 395 (6704), 801–804. https://doi.org/10.1038/27441.
Menegas, W., Bergan, J.F., Ogawa, S.K., Isogai, Y., Umadevi Venkataraju, K., Osten, P., Uchida, N., Watabe-Uchida, M., 2015. Dopamine neurons projecting to the posterior striatum form an anatomically distinct subclass. eLife 4, e10032. https://doi.org/10.7554/eLife.10032.
van der Merwe, R.K., Nadel, J.A., Copes-Finke, D., Pawelko, S., Scott, J.S., Ghanem, M., Fox, M., Morehouse, C., McLaughlin, R., Maddox, C., Albert-Lyons, R., Malaki, G., Groce, V., Turocy, A., Aggadi, N., Jin, X., Howard, C.D., 2023. Characterization of striatal dopamine projections across striatal subregions in behavioral flexibility. Eur. J. Neurosci. https://doi.org/10.1111/ejn.15910.
Mongia, S., Yamaguchi, T., Liu, B., Zhang, S., Wang, H., Morales, M., 2019. The ventral tegmental area has calbindin neurons with the capability to co-release glutamate and dopamine into the nucleus accumbens. Eur. J. Neurosci. 50 (12), 3968–3984. https://doi.org/10.1111/ejn.14493.
Moy, S.S., 1995. Impaired acquisition and operant responding after neonatal dopamine depletion in rats. Pharmacol. Biochem. Behav. 52 (2), 433–441. https://doi.org/10.1016/0091-3057(95)00136-K.
Moy, S.S., Criswell, H.E., Breese, G.R., 1997. Differential effects of bilateral dopamine depletion in neonatal and adult rats. Neurosci. Biobehav. Rev. 21 (4), 425–435. https://doi.org/10.1016/S0149-7634(96)00040-1.
Nandhagopal, R., Kuramoto, L., Schulzer, M., Mak, E., Cragg, J., Lee, C.S., McKenzie, J., McCormick, S., Samii, A., Troiano, A., Ruth, T.J., Sossi, V., de la Fuente-Fernandez, R., Calne, D.B., Stoessl, A.J., 2009. Longitudinal progression of sporadic Parkinson's disease: a multi-tracer positron emission tomography study. Brain: A J. Neurol. 132 (Pt 11), 2970–2979. https://doi.org/10.1093/brain/awp209.
Niv, Y., Daw, N.D., Joel, D., Dayan, P., 2007. Tonic dopamine: opportunity costs and the control of response vigor. Psychopharmacology 191 (3), 507–520. https://doi.org/10.1007/s00213-006-0502-4.

Panman, L., Papathanou, M., Laguna, A., Oosterveen, T., Volakakis, N., Acampora, D., Kurtsdotter, I., Yoshitake, T., Kehr, J., Joodmardi, E., Muhr, J., Simeone, A., Ericson, J., Perlmann, T., 2014. Sox6 and Otx2 control the specification of substantia nigra and ventral tegmental area dopamine neurons. Cell Rep. 8 (4), 1018–1025. https://doi.org/10.1016/j.celrep.2014.07.016.

Parker, N.F., Cameron, C.M., Taliaferro, J.P., Lee, J., Choi, J.Y., Davidson, T.J., Daw, N. D., Witten, I.B., 2016. Reward and choice encoding in terminals of midbrain dopamine neurons depends on striatal target. Nat. Neurosci. 19 (6), 845–854. https://doi.org/10.1038/nn.4287.

Pausch, C., Schomburg, R., Wagenpfeil, S., Wollenweber, F.A., Bayer, C., Fassbender, K., Behnke, S., 2016. Neuropsychological impairment in prodromal Parkinson's disease. J. Neurol. Sci. 371, 117–120. https://doi.org/10.1016/j.jns.2016.10.007.

Peterson, D.A., Elliott, C., Song, D.D., Makeig, S., Sejnowski, T.J., Poizner, H., 2009. Probabilistic reversal learning is impaired in Parkinson's disease. Neuroscience 163 (4), 1092–1101. https://doi.org/10.1016/j.neuroscience.2009.07.033.

Phillips, P.E.M., Stuber, G.D., Heien, M.L.A.V., Wightman, R.M., Carelli, R.M., 2003. Subsecond dopamine release promotes cocaine seeking. Nature 422 (6932), 614–618. https://doi.org/10.1038/nature01476.

Picconi, B., Centonze, D., Håkansson, K., Bernardi, G., Greengard, P., Fisone, G., Cenci, M.A., Calabresi, P., 2003. Loss of bidirectional striatal synaptic plasticity in L-DOPA–induced dyskinesia. Nat. Neurosci. 6 (5) https://doi.org/10.1038/nn1040. Article 5.

Pickel, V.M., Joh, T.H., Reis, D.J., 1977. Regional and ultrastructural localization of tyrosine hydroxylass by immunocytochemistry in dopaminergic neurons of the mesolimbic and nigroneostriatal systems. Adv. Biochem. Psychopharmacol. 16, 321–329.

Poulin, J.-F., Zou, J., Drouin-Ouellet, J., Kim, K.-Y.A., Cicchetti, F., Awatramani, R.B., 2014. Defining midbrain dopaminergic neuron diversity by single-cell gene expression profiling. Cell Rep. 9 (3), 930–943. https://doi.org/10.1016/j.celrep.2014.10.008.

Poulin, J.-F., Caronia, G., Hofer, C., Cui, Q., Helm, B., Ramakrishnan, C., Chan, C.S., Dombeck, D.A., Deisseroth, K., Awatramani, R., 2018. Mapping projections of molecularly defined dopamine neuron subtypes using intersectional genetic approaches. Nat. Neurosci. 21 (9), 1260–1271. https://doi.org/10.1038/s41593-018-0203-4.

Poulin, J.-F., Gaertner, Z., Moreno-Ramos, O.A., Awatramani, R., 2020. Classification of midbrain dopamine neurons using single-cell gene expression profiling approaches. Trends Neurosci. 43 (3), 155–169. https://doi.org/10.1016/j.tins.2020.01.004.

Rizzi, G., Tan, K.R., 2017. Dopamine and acetylcholine, a circuit point of view in Parkinson's disease. Front. Neural Circ. 11, 110. https://doi.org/10.3389/fncir.2017.00110.

Robinson, T.E., Whishaw, I.Q., 1988. Normalization of extracellular dopamine in striatum following recovery from a partial unilateral 6-OHDA lesion of the substantia nigra: a microdialysis study in freely moving rats. Brain Res. 450 (1), 209–224. https://doi.org/10.1016/0006-8993(88)91560-0.

Root, D.H., Wang, H.-L., Liu, B., Barker, D.J., Mód, L., Szocsics, P., Silva, A.C., Maglóczky, Z., Morales, M., 2016. Glutamate neurons are intermixed with midbrain dopamine neurons in nonhuman primates and humans. Sci. Rep. 6 (1) https://doi.org/10.1038/srep30615. Article 1.

Ross, G.W., Petrovitch, H., Abbott, R.D., Nelson, J., Markesbery, W., Davis, D., Hardman, J., Launer, L., Masaki, K., Tanner, C.M., White, L.R., 2004. Parkinsonian signs and substantia nigra neuron density in decendents elders without PD. Ann. Neurol. 56 (4), 532–539. https://doi.org/10.1002/ana.20226.

Rylander, D., Parent, M., O'Sullivan, S.S., Dovero, S., Lees, A.J., Bezard, E., Descarries, L., Cenci, M.A., 2010. Maladaptive plasticity of serotonin axon terminals in levodopa-induced dyskinesia. Ann. Neurol. 68 (5), 619–628. https://doi.org/10.1002/ana.22097.

Salamone, J.D., Correa, M., 2012. The mysterious motivational functions of mesolimbic dopamine. Neuron 76 (3), 470–485. https://doi.org/10.1016/j.neuron.2012.10.021.

Saunders, B.T., Richard, J.M., Margolis, E.B., Janak, P.H., 2018. Dopamine neurons create Pavlovian conditioned stimuli with circuit-defined motivational properties. Nat. Neurosci. 21 (8), 1072–1083. https://doi.org/10.1038/s41593-018-0191-4.

Schallert, T., Petrie, B.F., Whishaw, I.Q., 1989. Neonatal dopamine depletion: spared and unspared sensorimotor and attentional disorders and effects of further depletion in adulthood. Psychobiology 17 (4), 386–396. https://doi.org/10.3758/BF03337798.

Schultz, W., 2007. Multiple dopamine functions at different time courses. Annu. Rev. Neurosci. 30 (1), 259–288. https://doi.org/10.1146/annurev.neuro.28.061604.135722.

Schultz, W., Dayan, P., Montague, P.R., 1997. A neural substrate of prediction and reward. Science 275 (5306), 1593–1599. https://doi.org/10.1126/science.275.5306.1593.

Seiler, J.L., Cosme, C.V., Sherathiya, V.N., Schaid, M.D., Bianco, J.M., Bridgemohan, A. S., Lerner, T.N., 2022. Dopamine signaling in the dorsomedial striatum promotes compulsive behavior. Curr. Biol. 32 (5), 1175–1188.e5. https://doi.org/10.1016/j.cub.2022.01.055.

da Silva, J.A., Tecuapetla, F., Paixão, V., Costa, R.M., 2018. Dopamine neuron activity before action initiation gates and invigorates future movements. Nature 554 (7691), 244–248. https://doi.org/10.1038/nature25457.

Sofroniew, N.J., Flickinger, D., King, J., Svoboda, K., 2016. A large field of view two-photon mesoscope with subcellular resolution for in vivo imaging. eLife 5, e14472. https://doi.org/10.7554/eLife.14472.

Somayaji, M., Cataldi, S., Choi, S.J., Edwards, R.H., Mosharov, E.V., Sulzer, D., 2020. A dual role for α-synuclein in facilitation and depression of dopamine release from substantia nigra neurons in vivo. Proc. Natl. Acad. Sci. 117 (51), 32701–32710. https://doi.org/10.1073/pnas.2013652117.

Steinkellner, T., Conrad, W.S., Kovacs, I., Rissman, R.A., Lee, E.B., Trojanowski, J.Q., Freyberg, Z., Roy, S., Luk, K.C., Lee, V.M., Hnasko, T.S., 2022. Dopamine neurons exhibit emergent glutamatergic identity in Parkinson's disease. Brain 145 (3), 879–886. https://doi.org/10.1093/brain/awab373.

Surmeier, D.J., Schumacker, P.T., 2013. Calcium, bioenergetics, and neuronal vulnerability in Parkinson's disease *. J. Biol. Chem. 288 (15), 10736–10741. https://doi.org/10.1074/jbc.R112.410530.

Surmeier, D.J., Obeso, J.A., Halliday, G.M., 2017. Selective neuronal vulnerability in Parkinson disease. Nat. Rev. Neurosci. 18 (2), 101–113. https://doi.org/10.1038/nrn.2016.178.

Swainson, R., Rogers, R.D., Sahakian, B.J., Summers, B.A., Polkey, C.E., Robbins, T.W., 2000. Probabilistic learning and reversal deficits in patients with Parkinson's disease or frontal or temporal lobe lesions: possible adverse effects of dopaminergic medication. Neuropsychologia 38 (5), 596–612. https://doi.org/10.1016/S0028-3932(99)00103-7.

Tanaka, H., Kannari, K., Maeda, T., Tomiyama, M., Suda, T., Matsunaga, M., 1999. Role of serotonergic neurons in L-DOPA-derived extracellular dopamine in the striatum of 6-OHDA-lesioned rats. Neuroreport 10 (3), 631–634. https://doi.org/10.1097/00001756-199902250-00034.

Tanguay, W., Ducrot, C., Giguère, N., Bourque, M.-J., Trudeau, L.-E., 2021. Neonatal 6-OHDA lesion of the SNc induces striatal compensatory sprouting from surviving SNc dopaminergic neurons without VTA contribution. Eur. J. Neurosci. 54 (7), 6618–6632. https://doi.org/10.1111/ejn.15437.

Thorn, C.A., Atallah, H., Howe, M., Graybiel, A.M., 2010. Differential dynamics of activity changes in dorsolateral and dorsomedial striatal loops during learning. Neuron 66 (5), 781–795. https://doi.org/10.1016/j.neuron.2010.04.036.

Tian, J., Huang, R., Cohen, J.Y., Osakada, F., Kobak, D., Machens, C.K., Callaway, E.M., Uchida, N., Watabe-Uchida, M., 2016. Distributed and mixed information in monosynaptic inputs to dopamine neurons. Neuron 91 (6), 1374–1389. https://doi.org/10.1016/j.neuron.2016.08.018.

Torres, E.B., Heilman, K.M., Poizner, H., 2011. Impaired endogenously evoked automated reaching in Parkinson's disease. J. Neurosci. 31 (49), 17848–17863. https://doi.org/10.1523/JNEUROSCI.1150-11.2011.

Tsutsui-Kimura, I., Matsumoto, H., Akiti, K., Yamada, M.M., Uchida, N., Watabe-Uchida, M., 2020. Distinct temporal difference error signals in dopamine axons in three regions of the striatum in a decision-making task. eLife 9, e62390. https://doi.org/10.7554/eLife.62390.

Venda, L.L., Cragg, S.J., Buchman, V.L., Wade-Martins, R., 2010. α-Synuclein and dopamine at the crossroads of Parkinson's disease. Trends Neurosci. 33 (12), 559–568. https://doi.org/10.1016/J.TINS.2010.09.004.

Wang, L.P., Li, F., Wang, D., Xie, K., Wang, D., Shen, X., Tsien, J.Z., 2011. NMDA receptors in dopaminergic neurons are crucial for habit learning. Neuron 72 (6), 1055–1066. https://doi.org/10.1016/j.neuron.2011.10.019.

Warlow, S.M., Singhal, S.M., Hollon, N.G., Faget, L., Dowlat, D.S., Zell, V., Hunker, A.C., Zweifel, L.S., Hnasko, T.S., 2023. Mesoaccumbal glutamate neurons drive reward via glutamate release but aversion via dopamine co-release. Neuron. https://doi.org/10.1016/j.neuron.2023.11.002.

Watabe-Uchida, M., Zhu, L., Ogawa, S.K., Vamanrao, A., Uchida, N., 2012. Whole-brain mapping of direct inputs to midbrain dopamine neurons. Neuron 74 (5), 858–873. https://doi.org/10.1016/j.neuron.2012.03.017.

Wu, J., Kung, J., Dong, J., Chang, L., Xie, C., Habib, A., Hawes, S., Yang, N., Chen, V., Liu, Z., Evans, R., Liang, B., Sun, L., Ding, J., Yu, J., Saez-Atienzar, S., Tang, B., Khaliq, Z., Lin, D.-T., Cai, H., 2019. Distinct connectivity and functionality of aldehyde dehydrogenase 1a1-positive nigrostriatal dopaminergic neurons in motor learning. Cell Rep. 28 (5), 1167–1181.e7. https://doi.org/10.1016/j.celrep.2019.06.095.

Yagishita, S., Hayashi-Takagi, A., Ellis-Davies, G.C.R., Urakubo, H., Ishii, S., Kasai, H., 2014. A critical time window for dopamine actions on the structural plasticity of dendritic spines. Science (New York, N.Y.) 345 (6204), 1616–1620. https://doi.org/10.1126/science.1255514.

Yamada, T., McGeer, P.L., Baimbridge, K.G., McGeer, E.G., 1990. Relative sparing in Parkinson's disease of substantia nigra dopamine neurons containing calbindin-D28K. Brain Res. 526 (2), 303–307. https://doi.org/10.1016/0006-8993(90)91236-a.

Yin, H.H., Knowlton, B.J., Balleine, B.W., 2004. Lesions of dorsolateral striatum preserve outcome expectancy but disrupt habit formation in instrumental learning. Eur. J. Neurosci. 19 (1), 181–189. https://doi.org/10.1111/j.1460-9568.2004.03095.x.

Yin, H.H., Ostlund, S.B., Knowlton, B.J., Balleine, B.W., 2005. The role of the dorsomedial striatum in instrumental conditioning. Eur. J. Neurosci. 22 (2), 513–523. https://doi.org/10.1111/j.1460-9568.2005.04218.x.

Ztaou, S., Amalric, M., 2019. Contribution of cholinergic interneurons to striatal pathophysiology in Parkinson's disease. Neurochem. Int. 126, 1–10. https://doi.org/10.1016/j.neuint.2019.02.019.

Zweifel, L.S., Argilli, E., Bonci, A., Palmiter, R.D., 2008. Role of NMDA receptors in dopamine neurons for plasticity and addictive behaviors. Neuron 59 (3), 486–496. https://doi.org/10.1016/j.neuron.2008.05.028.